UNIVERSITY OF OKLAHOMA MEDICAL CENTER

ROLE OF THE VEINS IN SHOCK

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Technical Report No. 7
University of Oklahoma Medical Center THRMIS Contract

MEDICAL CENTER RESEARCH AND DEVELOPMENT OFFICE
OF THE UNIVERSITY OF OKLAHOMA FOUNDATION, INC.
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October 21, 1969

Research sponsored by the Office of Naval Research
Contract N00014-68-A-0496
Project NR 105-516

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Extensive work in recent years has shed much light on the function of veins under a variety of conditions. Several important review articles have focused on the many problems concerning mechanisms operating in the venous system.[1,2,3] Present knowledge about the control of veins is fragmentary regarding, in particular, local and reflex as well as central nervous control.[1] It is not true that the veins are a passive system of draining tubes; the venous system appears to be as reactive and well controlled as any of the other vascular segments.[1] Veins seem to have at least two major dynamic functions: resistance and capacitance functions, which are influenced by direct passive and active (neurohumoral), and indirect factors.

Veins transmit blood from capillaries to the right atrium in the systemic circulation and any factor, passive or active, influencing passage of blood through this segment will alter cardiac output directly. Cardiac output is equal to venous return under steady state conditions, and any situation which alters the capacitance or resistance functions of veins may be expected to alter cardiac output. Although the magnitude of venous resistance changes is very small when compared to the total contribution of pre-capillary vascular segments, its physiological importance cannot be minimized. For example, if venous pressure increases in a particular vascular bed, a rise in organ weight may take place, even with a large vein pressure elevation of only 1 mm Hg,[4] and capillary pressure may rise resulting in loss of fluid to the extravascular space or pooling upstream from constricted veins. Thus, a slight increase in venous resistance, under certain conditions, could result in loss of blood from the active circulation, a decrease in venous return

and subsequent drop in cardiac output. This, of course, assumes that no other changes intervene in response to the increase in venous pressure which could conceivably precipitate a variety of other actions. Of course, one cannot consider the contribution of the venous resistance component to intravascular pooling or extravascular loss of fluid, without also taking into account changes occurring in the pre-capillary vascular segment. For example, changes in capillary mean hydrostatic pressure depend on alterations in the ratio between pre-capillary and post-capillary resistance segments. Thus, if the ratio of pre-capillary to post-capillary resistance is increased, mean capillary hydrostatic pressure will fall, leading to a net absorption of extravascular fluid to the circulation, and the opposite will occur when the ratio is decreased.[1] Changes in this ratio constitute one of the main physiologic variables in the filtration exchange. Because of the physical proximity of veins to capillaries, and on account of the relative ease by which pressure can be transmitted upstream through the venous system even though the absolute value of venous resistance is small compared to that of the arterioles, the post-capillary resistance segment may exercise a profound influence on the capillary bed.

A normal physiological function of veins is their ability to store blood, described as their capacitance function. It is designated thusly because it contains some 65 to 80 percent of the entire blood volume.[5,6] It, therefore, constitutes a voluminous and highly variable blood reservoir or cardiac "forechamber." Folkow and Mellander discuss the integrated function of veins and outline various features which must be taken into consideration in its understanding: (1) the functional characteristics of

venous smooth muscle; (2) the superimposed nervous and hormonal influences; (3) reflex and central control; and (4) the cooperation and/or competition between neurogenic mechanisms and local factors which influence venous tone.

Mellander and Lewis[7] point out that previous studies on the peripheral circulation in shock have been restricted almost exclusively to descriptions of the changes in resistance to blood flow. They add that a complete analysis must also take into account the concommitant effect of shock on capacitance, the relative size of the capillary bed open to flow, and the rate and direction of capillary filtration.

The purpose of this paper is to allude to our present knowledge describing changes in function or activity of the venous system and to develop an analysis of these observations leading to a mechanistic understanding of the role of veins in shock.

Neural influences on the venous system in shock. During hemorrhagic shock, there is impairment and eventually abolition of the responses of the capacitance vessels in cat skeletal muscle to regional lumbar sympathetic vasoconstrictor nerve fiber stimulation.[7] Also, the pre-capillary resistance response declines faster and is abolished earlier than the post-capillary resistance response. The effect of this is to impair and eventually abolish the ability of constrictor nerve stimulation to decrease mean capillary hydrostatic pressure. Preservation of the post-capillary response beyond that of the pre-capillary, eventually results in a net outward movement of capillary fluid in response to nerve stimulation. In cats, two hours after onset of hemorrhage, the rate of loss of plasma filtrate from the circulation is reported to be 0.035 ml/min/100 gms of

tissue.[7] This amount is considerable and in a 70 kg man could conceivably result in a decrease in circulating blood volume of 600 ml/hour. This would be accomplished by filtering only 2 ml of fluid into the interstitial space of every 100 gms of muscle, a volume not detected as gross edema.[7] Stimulation of the sympathetic outflow to the extremities of dogs produces marked and prolonged elevations in small vein pressure.[8,9,10] One of the major problems is that since only alpha receptors are present in veins, sympathetic nerve stimulation results only in constriction.[3] Relative relaxation of the pre-capillary segment might therefore be deleterious from the standpoint of trapping blood in the periphery. In the normal physiological state, contraction of venous smooth muscle is of hemodynamic significance either by its ability to mobilize blood and thus promote venous return to the heart, or by its ability to stiffen the walls of the veins and so enable them to resist a greater hydrostatic pressure.[11] The latter type of contraction also helps to maintain venous return by preventing or reducing pooling of blood.

Humoral influences on the venous system in shock. This section will be concerned with the vascular effects of endogenously released humoral agents such as histamine and catecholamines and metabolic products, including a variety of unknown substances released during normal metabolism from the tissue cells. Hemorrhagic hypotension is associated with a marked reduction in skeletal muscle blood flow, which may result in a relative imbalance between the supply of blood and the metabolic demands of the tissue. In this situation, it is assumed that there is a relative accumulation of tissue metabolites,[7] which results in dilatation of vascular

smooth muscle. Even the venous segment participates in dilatation although pre-capillary vessels show a greater degree of relaxation. Current research in this laboratory has utilized a modification of the Pappenheimer and Soto-Rivera technique[4] in determining isogravimetric capillary pressure. With this technique average capillary pressure in the foreleg can be determined. Pre-capillary resistance may then be calculated by determining the difference between large limb artery pressure and mid-capillary pressure and dividing this difference by the blood flow ($R_a = P_a - P_c/F$) while post-capillary resistance may be estimated by determining the difference between mid-capillary pressure and orifice vein pressure and dividing this difference by the blood flow ($R_v = P_c - P_v/F$). Experiments carried out in this laboratory utilizing the technique have clearly shown that the pre-capillary segment (large artery to capillary) is very sensitive to the dilating effects of histamine infusion.[12] The post-capillary segment (capillary to orifice vein) does not respond to histamine infusion by resistance changes, except with very high doses in which the results are variable.

Research on gram-negative endotoxin shock in dogs has demonstrated profound hepatic venous constriction.[13,14] Intravenous injection of endotoxin from Escherichia coli in dogs is characterized by an immediate and precipitous decline in blood pressure with a simultaneous elevation of portal vein pressure. This reaction is abolished by hepatectomy, or exclusion of the liver from the circulation, and was found to be due primarily to trapping of blood within the liver. Following intravenous injection of E. coli endotoxin, marked increases in portal venous pressure occur and as a result venous return to the right heart is drastically reduced resulting in systemic

hypotension. The rise in portal vein pressure occurs passively as a result of intrahepatic venous constriction. A catheter advanced retrograde into the hepatic vein with a tip placed within the liver substance was found to exhibit a pressure rise as a result of endotoxin injection. This earlier work suggested that localized venous spasm in the hepatic venous system produced pooling of large quantities of blood. The total venous return was thereby critically reduced and a fall in cardiac output and arterial blood pressure were inevitable and would result in severe systemic hypotension and shock. To clarify the role of the liver in forms of shock, a series of studies has been carried out in this laboratory with the isolated perfused dog liver.[15] Evidence from this study pointed to the intrahepatic venous system as the primary site of endotoxin action with a subsequent myogenic response in the hepatic arterial segment. Results from studies on the isolated liver further show that the initial vascular responses of the liver to endotoxin do not depend on the release of agents from extra-hepatic sites, since the response of the isolated perfused liver occurs in advance of recirculation time and responses of the liver perfused by a heart-lung preparation or by a dog are indistinguishable. Data suggest that the liver is the primary site for the initial action of endotoxin. Venous responses to endotoxin of the isolated denervated organ were similar to those seen in the intact innervated organ. Endotoxin injection into either hepatic artery or portal vein systems resulted in a rapidly developing venoconstriction, presumably in the post-sinusoidal region deep within the venous vasculature. Hepatic vein pressures recorded from catheters placed retrograde into deep veins show significant rises

after endotoxin. Several suggested mechanisms of action regarding the liver venous response to endotoxin emerge from this study. Endotoxin may exert a direct action on the hepatic veins. This possibility was supported by the observations that no vasoactive drug or combination of drugs injected into the inflow hepatic vessels satisfactorily duplicated the vascular response of the liver to endotoxin. It may be, however, that vasoactive agents which are as yet unidentified are instrumental in producing the liver vascular response to endotoxin. Of great interest in the present study was the observation that the vascular response of the liver was the same whether drugs were injected into hepatic artery or portal vein inflow vessels. This finding suggested (1) that extensive and anastomotic channels exist between arteries and veins, or (2) that arteriolar segments are bathed in venous blood. Endotoxin may act by releasing endogenous vasoactive agents within the liver resulting in vasoconstriction of intra-hepatic venules. If vasoconstrictor substances are released, their concentrations in venous blood must be very low since the leg bioassay device ordinarily responded with only a slight dilator response; however, it is possible that vasoactive agents may be released in close proximity to the vascular smooth muscle acting specifically in this region, not being released into the general circulation in significant concentration.[15]

Not only are the veins of the hepatic bed directly involved in the shock reaction in the dog, but intestinal veins and venules also participate in the response to endotoxin as has been shown by Meyer and Visscher.[16] These investigators determined the hemodynamic responses of intestinal vascular segments of the dog to intravenous injection of a lethal dose

of E. coli endotoxin. Pressures were measured in large and small vessels of the intestine and mesentery (small veins 30-60 μ in radius). Mesenteric small vein pessures were obtained by using plastic cannulas with outside diameters of 0.5 to 0.6 mm for the small vessels. In another group of animals, pressures were measured in the intestinal small veins (66-120 μ in diameter) utilizing a microcannulation technique. Cannulas were kept patent by periodic flushing with heparinized saline. Pressures were measured by Statham pressure transducers and recorded with a meaning circuit on a Sanborn recorder. The submucosal vessels of the small intestine were exposed by microdissection in seven animals. Microscopic observations were made with a Leitz Ultropak and photographed with a 35-mm Leica camera. Loops of small intestine were placed on a cork platform, covered with a polyvinyl sheet, and irrigated with Ringer's solution. Vascular diameters were determined five times at a given site to allow statistical treatment of the error of measurement of vessels in a particular photomicrograph. Venous blood pressures were also measured in this experimental group. Meyer and Visscher discussed the possible effects of the various surgical procedures on the nerve supply to blood vessels in the above technique. They assumed that most vasomotor nerves followed major arterial and venous trunks. They, therefore, supposed that the use of a branch of a mesenteric artery supplying a portion of the intestine not under study would presumably not involve interference with a nerve supply to structures under observation. In the case of small vein cannulation by plastic catheters ligated in place, there was, the authors stated, a disturbance of a nerve supply to a small part of the

vascular bed, but the objective in these cases was to measure pressures in the collateral vessels in which the nerve supply was intact. They further stated that it probably was the case that all of the pressures measured in this way were somewhat lower than they would have been to be in vessels of the same size with free-flowing blood, but no other method was available for long-term observation, and they readily accepted this defect. It was believed that any defects due to this experimental procedure would be systematic in the sense that the direction and proportionate magnitude of the error would probably be the same at all times. Microscopic findings showed, on the average, that the small veins and venules were increased significantly in diameter only at two minutes during the initial phase of elevated portal vein pressure following endotoxin injection. The veins, however, became significantly smaller at 50 and 60 minutes. Photomicrographs showed areas of localized venous constriction during the initial phase, but these areas became much more numerous during the later stages of shock. After endotoxin, from the data on fractional pressure drop, it was evident that the resistance rises in the small vein to portal vein segment. This was followed by declined in resistance in this segment, yet during the secondary shock period there was a further rise in resistance in the small vein to portal vein segment. Meyer and Visscher also calculated venous wall tension (T) according to the Laplace equation, $T = Pr$, where P is a transmural pressure and r the radius of the vessel. The wall tension in the small veins can be approximated by combining the measurements of venous pressures in the intestinal small vein and the changes in radius of veins with similar initial dimensions. These authors presented an average normalized tension-radius diagram at various times after endotoxin. They showed that venous

wall tension rose during the portal hypertensive phase and remained above control levels throughout the period of observation. The initial wall tensions in the small veins, or venules, were computed to be 74 dynes/cm before endotoxin was injected. At 50 minutes during the shock period, the values calculated were 92 dynes/cm for the small veins. It has been pointed out that the mechanism for the trapping of blood in the liver and the intestine during the early stages after endotoxin involved the contraction of the hepatic vein or venule sphincters. The mechanism of later intestinal pooling of blood was not known. The results of Meyer and Visscher[16] suggest that the mechanism for the pooling of blood and tissue fluid during the later stages of endotoxin shock involves the development of active tension in the intestinal small veins.

Further work has been carried out by Hinshaw and Nelson[17] on the venous response of the intestine to endotoxin. These authors studied the response of the canine intestine to endotoxin by utilizing an isolated perfused segment of small bowel established in series with an adult dog intravenously anesthetized with sodium pentobarbital. A loop of small intestine from a donor dog was dissected free, together with its connection to the superior mesenteric artery and aorta, and perfused at constant flow in a retrograde fashion via the abdominal aorta. Plastic cannulas were secured in each end of the loop to allow for drainage, and mesenteric small-vein pressures (outside diameter > 0.7 mm) were obtained via retrograde cannulation. Small plastic catheters were advanced in a retrograde direction from the larger mesenteric veins toward the smaller veins. The catheter tip was not wedged, as evidenced by a rapid drop in pressure

when saline was injected through the catheter and a ready withdrawal of blood from the catheter. The large orifice vein of the isolated intestine was severed and drained at atmospheric pressure. Changes in intestinal weight were continuously monitored by means of a strain gauge weighing device. Lethal doses of E. coli endotoxin were administered via the perfusion dog in all experiments. This study elucidated the action of endotoxin on the intestine and illustrated the causal mechanism between circulating vasoactive agents and the increase in intestinal weight. Results from this study by Hinshaw and Nelson showed that increases in venous segment resistance and intestinal weight were found during the post-endotoxin period. Since pressure of the orifice mesenteric vein was maintained at 0 mm Hg, increases in small vein pressure indicated a rise in venous segment resistance in the experiments carried out by Hinshaw and Nelson. Pooling in the intestines after endotoxin need not, therefore, be explained on the basis of back-pressure effects from the hepatic venous circulation, or cytotoxic changes in the capillary membrane, but may be accounted for by the presence of sustained small-vein constriction in the splanchnic bed. These findings demonstrated the prominent part performed by peripheral small veins in endotoxin shock. These investigators also assayed the relative responsiveness of small veins to injected epinephrine before and after endotoxin. Venous responsiveness in their experiments was expressed in terms of total area above base-line values measured after intra-arterial injections of epinephrine into the intestinal inflow circuit. Their results showed that small intestinal veins, though

not always showing a greater aptitude in response to epinephrine after endotoxin, invariably remained constricted for a longer period. After injection of epinephrine, the time required for small veins to return to their pre-injected pressure values was greatly increased by endotoxin. In summary, evidence indicates that the progressive development of splanchnic pooling is primarily due to active constriction of small veins in which their responsiveness to epinephrine is enhanced by endotoxin.

It should be pointed out that the previous findings were reported from the dog given endotoxin. Numerous species differences have been discovered in subsequent research. The first clear-cut description of species differences in shock was reported by Kuida and others.[18] In this regard, species differences in the hepatic venous response to endotoxin should be evaluated. The subsequent study by Kuida's group conclusively demonstrated a difference in the early hemodynamic effects of endotoxin in the cat, rabbit, and monkey as compared with those which occur in the dog. The minimal and inconsistent changes in weight of short segments of gut in the monkey, rabbit, and cat, combined with the slight to moderate increment in portal venous pressure and the markedly lesser degree of pooling in the cat venous return experiments, were decidedly different from the response that occurs in the dog. The relatively gradual development of hypotension that usually occurs in the monkey and rabbit thus do not appear to be explainable on the basis of hepatic venous constriction.

The effects of endotoxin on the pulmonary hemodynamics of dogs and cats have been studied in intact animals, open chest animals with and without control of cardiac output by an extracorporeal venous reservoir

pump system, and in isolated perfused continuously weighed lungs.[19] A major purpose in these experiments was to determine the role of pulmonary veins in endotoxin shock. Pressure in a small pulmonary vein was measured by passing a fine polyethylene catheter (1.2 mm outside diameter) out into a peripheral vein via the left atrium. If this catheter was advanced until it became wedged, a pressure identical to that in the pulmonary artery was recorded. If, then, it was withdrawn from the wedged position by a minute increment, a range of pressures was obtained between pulmonary arterial and left atrial pressure. An arbitrary intermediate level was chosen in their experiments in order to observe changes in downstream resistance at constant flow associated with venous constriction or dilatation. Resistance in the post-capillary segment of the lung, that is, venous segment resistance, was calculated by subtracting left atrial pressure from pulmonary artery wedge pressure and dividing this difference by the blood flow through the lungs. Pulmonary artery wedge pressure was chosen in these experiments because it afforded the best available approximation to pulmonary capillary pressure. Results from their experiments showed that the pulmonary vascular response to endotoxin in the dog is characterized predominantly by constriction of pulmonary venules and/or small veins. Numerous measurements of pressures in small pulmonary veins (< 2 mm bore) invariably showed a rise after administration of endotoxin, indicating an increase in resistance to flow in the veins of intermediate bore. Increases in pulmonary artery wedge pressure were also obtained, and these observations are considered to be of importance in

showing that the artery wedge pressure changes were due to venous segment resistance alterations and not to artifacts. The additional observation that the pressure in the larger pulmonary veins did not change while large alterations occurred in the smaller veins indicated that the constriction was more or less localized in the region of the venules and small veins. Although the responses in the several experiments were variable in magnitude, the results showed that, on the average, calculated pulmonary venous resistance accounted for a greater portion of the increase in total resistance than did arterial resistance.

The effects of histamine, 5-hydroxytryptamine, and epinephrine on pulmonary hemodynamics with particular reference to venous segment resistances were studied by Gilbert's group.[20] Their experimental model was the isolated perfused dog lung. The lung was perfused at constant flow while pressures were measured in the left atrium and in either the pulmonary artery wedge position or a small pulmonary vein. Venous segment resistance changes were inferred from the drop in pressure from the pulmonary artery wedge to the pulmonary vein. Changes in lung weight were recorded continuously. It was found that histamine caused an increase in lung weight was observed, presumably as a result of increased capillary blood content. The correlation coefficient between the change in lung weight and the change in venous resistance was + 0.791. Small pulmonary vein pressures rose after administration of epinephrine, norepinephrine, histamine and 5 HT. Their results serve to implicate these humoral agents in the venous response to endotoxin.

Recent unpublished experiments carried out in this laboratory have focused on the role of the pulmonary veins in endotoxin shock in the monkey. Studies were carried out utilizing the venous return preparation in which cardiac inflow is held constant. The venous catheter was advanced through the left atrium and inserted into a deep pulmonary vein. The tip of the catheter was not placed in the wedged position as evidenced by flushing and withdrawal characteristics. The shocking dose of endotoxin was injected into the right atrium. Within 1 to 2 minutes pulmonary vein pressure became elevated and, since pulmonary blood flow was maintained constant in this preparation, this indicated a rise in pulmonary venous pressure.

The role of the veins in the hepatosplanchnic bed and in the pulmonary circulation in shock has been discussed. Our attention will now be directed to the response of veins in peripheral vessels; namely, the skin and muscle regions. Haddy[21] has determined the effect of histamine on small and large vessel pressures in the dog foreleg. His experimental preparation has served as a model for subsequent experiments carried out on the canine foreleg by other investigators. He found that low rates of infusion of histamine into the brachial artery of the forelimb raises small venous pressure by arteriolar dilatation; whereas, high rates of infusion raised venous pressure both by arteriolar dilatation and venous constriction. He pointed out that venous constriction probably results both from a direct action of histamine and indirectly through an adrenal discharge as a result of systemic hypotension. His work clearly distinguishes between the direct actions of injected vasoactive agents on a regional bed and on indirect actions resulting from the effects of the agents on the organisms as a whole, in this instance, by causing an adrenal discharge. That the

venous constriction partly results from adrenal discharge is indicated by the fact that constriction begins following the fall of systemic arterial pressure and is partially abolished by adrenergic blockade. Furthermore, it is known that epinephrine and norepinephrine are venous constrictors even in low concentrations. The relative contributions of arteriolar dilatation and venous constriction to rise of small venous pressure in the forelimb likely vary depending upon degree and distribution of elevation of concentration of histamine. Venous pressure rises because of arteriolar dilatation when increase of concentration is local and slight. When the concentration of histamine is greatly elevated locally, but also slightly elevated generally, venous constriction of the forelimb probably becomes relatively more important than arteriolar dilatation. Arteriolar dilatation becomes less and less effective in rising small venous pressure by virtue of the fall in systemic arterial pressure as a result of histamine administration and partial disappearance of arteriolar dilatation. In addition, the direct constrictor effect of histamine on veins is aided by the constrictor action of an adrenal discharge.

Haddy's analysis[21] of the mechanism of the foreleg venous response to injected vasoactive agents has a direct application to shock. Although vasoactive agents may be released in the earlier phase of the shock period prior to the drop in arterial pressure, and may have direct influences on the venous segment of regional beds, ultimately systemic arterial pressure falls and hypotension is observed. Following the onset of hypotension in shock, the involvement of the sympathoadrenal system would be expected, and

further constrictor effect of the venous system would be obtained. Forelimb venous changes associated with the development of irreversible endotoxin shock have been reported.[22] In these experiments a series of isolated leg perfusions were carried out to obtain more definitive information as to the nature of the peripheral vascular response of the post-capillary segments to endotoxin. Adult mongrel dogs, anesthetized with sodium pentobarbital, were used in these experiments. The leg from a dog was completely severed and placed on a strain gauge weighing device. It was perfused at constant flow by means of a Sigmamotor pump obtaining blood from an intact neparinized animal. The findings of this study indicated the important effects of circulating substance on the venous resistance in the isolated perfused leg. The presence of an intact animal in the perfusion circuit was found to be essential in order to obtain and sustain response in the venous system following injection of endotoxin, and indicated a crucial role of humoral substances released in the intact animal, resulting in alterations of vascular resistance in the foreleg. As the dog became severely hypotensive, vasoactive substances were released into the blood, carried to the limb, and resulted in vascular changes. These observations with endotoxin shock therefore bear a similarity to those observed previously by Haddy with histamine injection. An isolated leg perfused by a heart-lung preparation responds with only minimal small vein constriction after endotoxin. However, with the introduction of the animal into the perfusion circuit, a large sustained venous constriction in the foreleg is observed. The constriction of the foreleg veins takes place primarily only after the drop in systemic arterial pressure. This investigation[22] also suggested that the development of the irreversible period of endotoxin shock might be due

in part to altered responses of the post-capillary venous segment to pressor, epinephrine-like substances. Subsequent experiments carried out in this laboratory have also shown a similar venous response during hemorrhage in dogs. Hinshaw and others[23] have studied the response of the monkey foreleg in endotoxin shock. The surprising and unexpected finding was that decreases in the monkey forearm weight and small vein pressure were observed, thereby, indicating the complete absence of venous constriction. These monkey studies indicated that humorally induced vasoconstriction after endotoxin may be insignificant when compared with the dog and again point to the complicating effects in interpretation and understanding of mechanisms due to species differences. It is possible, however, that in the late phase of shock, monkey forearm responses may ultimately show vasoconstriction; however, this possibility must await further investigation. As an extension of the previous studies on the isolated limb, further experiments have been carried out utilizing an isolated saphenous canine vein. The vein preparation was surgically removed from the hindlimbs of adult mongrel dogs anesthetized with sodium pentobarbital, and the vein was immediately transferred to an oxygenated saline bath maintained at 37°C. A Statham pressure transducer was utilized to record changes in vessel tension. A period of 15-30 minutes was required for relaxation of the contractile elements of the vein to occur, such that a constant base line could be recorded. Epinephrine (0.1 μg) was added to the bath to obtain a standard response curve of the isolated strip. Experiments were carried out by adding 100 μg of E. coli endotoxin to the bath containing 50 ml of perfusate. A reproducible response of the isolated saphenous vein was observed when endotoxin was

added to heparinized whole blood. Approximately 6 gms of tension was developed by the contracting vessel which was sustained for 6-9 minutes. A latent period of 30-60 seconds was characteristically observed between the addition of the endotoxin and the contraction of the vein. The response of the isolated vein to histamine (25 μg) in whole blood was compared with its response to endotoxin. The tension curves were remarkably similar where the important distinction that the lag period observed between addition of endotoxin and contraction of the vein was not seen with histamine. These interesting experiments carried out by Vick[24] further showed that endotoxin had no direct action on the vein strip, but implicated a vasoactive agent which was liberated following the administration of endotoxin.

Reflex influences involving the veins in shock. As has been pointed out in an earlier section, the administration of endotoxin to the canine species results in a prominent hepatic vein constriction, followed by immediate engorgement of the liver. At the same time, there is a marked increase in hepatic arterial resistance. It was thought to be of interest to investigate the possibility that there may be a connection between the rise in hepatic vein pressure and the increase in hepatic arterial resistance. To evaluate this possibility, experiments were carried out on the isolated perfused dog liver.[25] The liver was continuously weighed and perfused at constant flow with arterial blood through the hepatic artery and venous blood through the portal vein. Hepatic vein pressure was increased in steps by means of partial outflow obstruction with a screw clamp adjustment. Hepatic artery pressure was seen to increase in a profound fashion as a

function of elevated hepatic vein pressure. An increase in hepatic arterial segment resistance occurred, presumably on the basis of a myogenic response. The vascular segment between the hepatic and portal veins exhibited only passive changes as a result of increased venous transmural pressure. The peculiar arterial response would serve to decrease flow through the hepatic arterial system in the face of liver pooling and certain stress states previously observed in the canine species. As an illustration of the great potency of such a reflex, on the average the initial portal vein pressure was about 7 mm Hg. At the highest elevation, the pressure was approximately 25 mm Hg. This resulted in the hepatic arterial pressure increasing from an average of about 100 mm Hg to an average of approximately 170 mm Hg. During this period, the hepatic vein pressure increased on the average from -2 mm Hg to 24 mm Hg. These results, therefore, showed that the rise in portal vein pressure was simply a passive function of the increase in hepatic vein pressure, a total increase in pressure in the former being about 18 mm Hg. In marked contrast the increase in hepatic arterial pressure was approximately 70 mm Hg. These data strongly suggest that an increase in transmural pressure in the terminal hepatic arteriolar segment stimulates smooth muscle of this segment to contract in a typical myogenic (Bayliss) fashion. The influence of localized compression forces on the arterial segment as a result of accumulation of blood and extravascular fluid following hepatic vein pressure elevation cannot be completely excluded as a possible explanation. However, some experiments showed that liver weight had returned essentially to the control value following release of hepatic vein partial obstruction, and yet hepatic artery pressure remained above its control

value for several minutes. It is possible that endotoxin may elicit an active vasomotor response in certain liver vessels, particularly hepatic arterioles. Injection of endotoxin in either the hepatic artery or the portal vein, with constant flow perfusion of both systems, results in a significantly greater increase in hepatic artery pressure than in portal vein pressure. This peculiar response, duplicated by raising hepatic vein pressure by a partial outflow obstruction as previously described, suggests that endotoxin injection causes hepatic vein constriction, which in turn produces hepatic arteriolar constriction via a myogenic mechanism. The arterial constriction should reduce liver volume if narrowing of high resistance vessels was generalized, but this effect would be offset by excessive post-sinusoidal venous constriction.

Summary. Research in recent years has provided new information on the function of veins under a variety of conditions. The primary purpose of this paper was to allude to studies describing changes in fucntion or activity of the venous system in shock and to develop an analysis of these observations leading to a mechanistic understanding of the role of the vein in this form of stress. This review has emphasized the two major dynamic functions of veins; that is, resistance and capacitance functions, which are influenced by both passive and active factors. Because of the relative physical proximity of veins to capillaries, even small changes in venous segment resistance may have profound effects on the circulation. In addition, the great capacity of veins to store blood under normal conditions provides a potential mechanism for a large shift in volume from the active to

sequestered compartments of the blood volume. Analysis of published results shows that there is a dynamic interaction between venous resistance and capacitance functions. For example, preservation of the post-capillary (venous) response beyond that of the pre-capillary (arterial) response in shock eventually results in a net outward movement of capillary fluid from the vascular bed as well as an intravascular sequestration of blood upstream from constricted veins. However, the relationships between resistance and capacitance functions are often complex and depend on the degree of stress. An example of this is seen when the liver is stimulated by small amounts of epinephrine to release its sequestrated blood into the active circulation. In this instance, the diameter of the veins is decreased. However, if the dose of epinephrine is increased to higher levels, concentrations reported in severe shock, the exact opposite effect may occur and blood may be pooled in the liver vasculature by potent venous constriction.

A variety of experimental techniques has been developed to qualify the resistance and capacitance functions of the veins in shock. These procedures have been outlined and discussed in this paper. The interpretation of the results from these experimental procedures, of course, has been difficult, For example, it is not always possible to distinguish between pooling within the venous system and pooling within the capillary bed, as well as loss of fluid to the extravascular compartment. However, in the case of shock, histopathological findings may be incorporated to gain an understanding of the role of veins in their capacitance functions. Thus, in the case of endotoxin shock, the venous return preparation indicates a high degree of

pooling immediately after endotoxin injection. Histological examinations have also shown the veins to be greatly engorged with blood during this period. Another helpful technique to assay the capacitance role of veins is the sensitive weighing device which has shown a clearer relationship between venous constriction and increases in weight. For example, in the isolated perfused weighed canine intestine, small increases in weight were produced by small increases in venous pressure, while large increases in weight were observed following large increases in venous pressure. Such procedures provide a helpful means of determining both resistance and capacitance roles of veins and their interactions. Possible applications of the modified Pappenheimer-Soto-Rivera isogravimetric technique appear to be very promising in studies of the role of veins in shock. With this procedure, calculations of post-capillary resistance may be carried out by utilizing the technique to provide an estimate of capillary pressure as well as exiting vein pressure. Other techniques have been discussed in which small catheters have been placed in various regions of the venous system, and changes in pressures have been measured in shock. If, at the same time, flow through these regions is known, venous segment resistances may be calculated. Also, if organ systems may be weighed at the same time, relationships between venous resistance changes and capacitance functions may be assayed. Pressures in major veins may also be estimated by cannulation of side branches with the advance of small catheters to the wall of the large vessel. These procedures may have particular benefit in that the actual circulation through the large venous segment is relatively undisturbed. There is always the potential

problem of partial flow obstruction by the presence of a catheter in a stream of blood. Care must be taken not to wedge catheters into small blood vessels or to partially obstruct the flow of blood by utilizing large catheters placed in relatively small veins. In spite of all the potential difficulties in experimental techniques in evaluating the capacitance and resistance functions of veins, results from various laboratories have shown a high degree of consistency, and their findings have led to a greater understanding of the roles of veins in shock. Of course, the veins are not performing in an isolated fashion. Influences are projecting beyond themselves to other parts of the circulation; for example, as has been pointed out in the venous arteriolar reflex. Changes occurring both upstream and downstream from the venous segment may have profound effects on the veins. It is clearly evident that the neural, humoral, and reflex activities on the veins are very complex and widespread, and a better understanding of their inter-relationships within the venous system and between the veins and other portions of the vascular tree must await further investigation.

References

1. Folkow, B. and Mellander, S.: Veins and Venous Tone. Am. Heart J. 68: 397-408, 1964.

2. Franklin, L. J.: A Monograph on Veins. Charles C. Thomas, Springfield, Illinois, 1937, p. 410.

3. Wood, J. E.: The Venous System. Sci. Am. 218: 86-96, 1968.

4. Pappenheimer, J. and Soto-Rivera, A.: Effective Osmotic Pressure on the Plasma Proteins and Other Quantities Associated with the Capillary Circulation in the Hindlimbs of Cats and Dogs. Am. J. Physiol. 152: 471-491, 1948.

5. Green, H. D.: Circulatory System: Physical Principles. In Glasser, O.: Medical Physics, Vol. 2, Chicago, 1950, Year Book Publishers, Inc.

6. Wiedeman, M. P.: Dimensions of Blood Vessels from Distributing Artery to Collecting Vein. Circ. Res. 12: 375-378, 1963.

7. Mellander, S. and Lewis, D. H.: Effect of Hemorrhagic Shock on the Reactivity of Resistance and Capacitance Vessels and on Capillary Filtration Transfer in Cat Skeletal Muscle. Circ. Res. 13: 105-118, 1963.

8. Lee, J. S. and Visscher, M. B.: Microscopic Studies on Skin Blood Vessels in Relation to Sympathetic Nerve Stimulation. Am. J. Physiol. 190: 37-40, 1957.

9. Kelly, W. D. and Visscher, M. B.: Effect of Sympathetic Nerve Stimulation on Cutaneous Small Vein and Small Artery Pressures, Blood Flow and Hind-Paw Volume in the Dog. Am. J. Physiol. 185: 453-464, 1956.

10. Davis, D. L. and Hamilton, W. F.: Small Vessel Responses of The Dog Paw. Am. J. Physiol. 196: 1316-1321, 1959.

11. Mellander, S. and Johansson, B.: Control of Resistance Exchange, and Capacitance Functions in the Peripheral Circulation. Pharm. Rev. 20: 117-196, 1968.

12. Dietzel, W., Massion, W. H., and Hinshaw, L. B.: The Mechanism of Histamine-Induced Transcapillary Fluid Movement. Pflügers Arch. 309: 99-106, 1969.

13. MacLean, L. D. and Weil, M. H.: Hypotension (Shock) in Dogs Produced by Escherichia coli Endotoxin. Circ. Res. 4: 546-556, 1956.

14. Weil, M. H., MacLean, L. D., Visscher, M. B., and Spink, W. W.: Studies on the Circulatory Changes in the Dog Produced by Endotoxin from Gram-Negative Micro-Organisms. J. Clin. Invest. 35: 1191-1198, 1956.

15. Hinshaw, L. B., Reins, D. A., and Hill, R. J.: Responses of Isolated Liver to Endotoxin. Canad. J. Physiol. Pharm. 44: 529-541, 1966.

16. Meyer, M. W. and Visscher, M. B.: Partial Analysis of Segmental Resistances in Intestinal Vessels after Endotoxin. Am. J. Physiol. 202: 913-918, 1962.

17. Hinshaw, L. B. and Nelson, D. L.: Venous Response of Intestine to Endotoxin. Am. J. Physiol. 203: 870-872, 1962.

18. Kuida, H., Gilbert, R. P., Hinshaw, L. B., Brunson, J. G., and Visscher, M. B.: Species Differences in Effect of Gram-Negative Endotoxin on Circulation. Am. J. Physiol. 200: 1197-1202, 1961.

19. Kuida, H., Hinshaw, L. B., Gilbert, R. P., and Visscher, M. B.: Effect of Gram-Negative Endotoxin on Pulmonary Circulation. Am. J. Physiol. 192: 335-344, 1958.

20. Gilbert, R. P., Hinshaw, L. B., Kuida, H., and Visscher, M. B.: The Effects of Histamine, 5-Hydroxytryptamine and Epinephrine on Pulmonary Hemodynamics with Particular Reference to Arterial and Venous Segment Resistances. Am. J. Physiol. 194: 165-170, 1958.

21. Haddy, F. J.: Effect of Histamine on Small and Large Vessel Pressures in the Dog Foreleg. Am. J. Physiol. 198: 161-168, 1959.

22. Hinshaw, L. B., Vick, J. A., Jordan, M. M., and Wittmers, L. E.: Vascular Changes Associated with Development of Irreversible Endotoxin Shock. Am. J. Physiol. 202: 103-110, 1962.

23. Hinshaw, L. B., Brake, C. M., Emerson, T. E., Jr., Jordan, M. M., and Masucci, F. D.: Participation of Sympathoadrenal System in Endotoxin Shock. Am. J. Physiol. 207: 925-930, 1964.

24. Vick, J.: Trigger Mechanism of Endotoxin Shock. Am. J. Physiol. 206: 944-946, 1964.

25. Hinshaw, L. B., Reins, D. A., and Wittmers, L. E.: Venous Arteriolar Response in the Canine Liver. Proc. Soc. Exptl. Biol. Med. 118: 979-982, 1965.

Unclassified
Security Classification

DOCUMENT CONTROL DATA - R & D

(Security classification of title, body of abstract and indexing annotation must be entered when the overall report is classified)

1. ORIGINATING ACTIVITY (Corporate author)

Medical Center Research and Development Office of the University of Oklahoma Foundation, Inc.

2a. REPORT SECURITY CLASSIFICATION

Unclassified

2b. GROUP

Unclassified

3. REPORT TITLE

Role of the Veins in Shock

4. DESCRIPTIVE NOTES (Type of report and, inclusive dates)

Technical Report

5. AUTHOR(S) (First name, middle initial, last name)

Lerner B. Hinshaw, Ph.D.

6. REPORT DATE	7a. TOTAL NO. OF PAGES	7b. NO. OF REFS
October 21, 1969	27	25

8a. CONTRACT OR GRANT NO.	9a. ORIGINATOR'S REPORT NUMBER(S)
N00014-68-A-0496	
b. PROJECT NO. NR 105-516	7
c.	9b. OTHER REPORT NO(S) (Any other numbers that may be assigned this report)
d.	

10. DISTRIBUTION STATEMENT

This document has been approved for public release and sale; its distribution is unlimited.

11. SUPPLEMENTARY NOTES	12. SPONSORING MILITARY ACTIVITY
	Office of Naval Research

13. ABSTRACT

Research in recent years has provided new information on the function of veins under a variety of conditions. The primary purpose of this paper was to allude to studies describing changes in function or activity of the venous system in shock and to develop an analysis of these observations leading to a mechanistic understanding of the role of the veins in this form of stress. This review has emphasized the two major dynamic functions of veins; that is, resistance and capacitance functions, which are influenced by both passive and active factors. A variety of experimental techniques has been developed to qualify the resistance and capacitance functions of the veins in shock. These procedures have been outlined and discussed in this paper. It is clearly evident that the neural, humoral, and reflex activities on the veins are very complex and widespread, and a better understanding of their inter-relationships within the venous system and between the veins and other portions of the vascular tree must await further investigation.

DD FORM 1 NOV 65 1473 (PAGE 1)

S/N 0101-807-6811

Unclassified
Security Classification

A-31408